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Low-Dose Estrogen May Fight Breast Cancer

By Kathleen Doheny
HealthDay Reporter

WEDNESDAY, Dec. 7 (HealthDay News) -- It sounds like a paradox, and it is: Even though estrogen can trigger the growth of breast [cancer](#) cells, small doses of the hormone can also help kill tumor cells.

In fact, low-dose estrogen may help [breast cancer](#) patients who've become resistant to therapies that work by blocking the hormone.

Now, researchers investigating this puzzle say they've discovered how estrogen kills these resistant tumor cells.

"It's all counterintuitive," said V. Craig Jordan, the Alfred G. Knudson Chair of Cancer Research at the Fox Chase Cancer Center in Philadelphia. Jordan is widely hailed as the "father of [tamoxifen](#)" for his efforts in developing the estrogen-blocking drug that helps prevent [breast cancer recurrence](#).

If estrogen is given at a specific time, he said, "instead of stimulating the growth [of breast cancer cells], it sees these dysfunctional aberrant cancer cells and instead of telling them to grow, tells them to die."

Jordan's team has published a series of papers in the scientific literature over the last few years, showing that is in fact the case.

"Now, we have found out the mechanism," he said.

Reporting in the Dec. 7 issue of the *Journal of the National Cancer Institute*, Jordan's team found that the form of estrogen called [estradiol](#) induces cell death, or apoptosis, by activating a specific chemical pathway. This pathway is controlled by proteins on the membrane of the cells called mitochondria.

"We basically blow up the mitochondria with the estrogen," Jordan said.

The "blowing up" stimulates the release of a molecule called cytochrome c within the cell. Cytochrome c, in turn, activates several enzymes that initiate cell death.

The study was conducted using breast cancer cell lines resistant to estrogen withdrawal. These cells underwent cell death when treated with very small concentrations of estradiol. The estrogen was 100 percent effective in killing the cancer cells, Jordan said.

Kill rates were higher in cells treated with estradiol, compared to those treated with fulvestrant, an estrogen-blocker, or cells from an untreated control group. Jordan's team also injected estrogen-treated cancer cells into mice, resulting in complete tumor regression.

Typically, women with estrogen-receptor positive breast cancers are put on treatments that block estrogen, such as tamoxifen, fulvestrant or aromatase inhibitors. For some reason, women may become resistant to this long-term therapy, with some cells adapting and thriving, even when deprived of estrogen.

"The study gives clinicians reassurance that they might consider estrogen as another alternative therapy for women with advanced breast cancer who have grown resistant to aromatase inhibitors," said Dr. Christy Russell, associate professor of medicine at the University of Southern California Keck School of Medicine, Los Angeles, and national chair of the breast cancer advisory group of the American Cancer Society.

Jordan said his team hopes to start clinical trials involving low-dose estradiol soon. "This is a true example of things we find in the laboratory that we can apply to patients very quickly," he said.

Women with breast cancer who have undergone treatment and then are put on the estrogen-blocking therapies often stop responding, Jordan said. "About 50,000 women [in the U.S.] a year have this drug-resistance problem," he estimated. "We'd probably be able to help a third of those" with the estrogen treatment, he added.

It wouldn't require big doses, Jordan said. He estimated that a dose of about 1.5 milligrams a day, given for eight to 12 weeks, might overcome the resistance and kill the cancer cells. Conventional hormone-replacement therapy, when given more widely, typically involves 0.625 milligrams of estrogen daily.

Another expert, Dr. Ann Partridge, a medical oncologist specializing in breast cancer at the Dana-Farber Cancer Institute in Boston, applauded the study.

"The news here is they are figuring out the mechanism," she said. The other good news is that "a physiological dose (what the body would normally make) of estrogen can have an effect."

"This may be another strategy for the treatment of breast cancer," Partridge said.

SOURCES: V. Craig Jordan, OBE, Ph.D., D.Sc., vice president and research director for medical sciences, and Alfred G. Knudson Chair of Cancer Research, Fox Chase Cancer Center, Philadelphia; Ann Partridge, M.D., M.P.H., medical oncologist, Dana-Farber Cancer Center, Boston; Christy Russell, M.D., associate

professor, medicine, University of Southern California Keck School of Medicine, Los Angeles, and national chair, breast cancer advisory group, American Cancer Society; Dec. 7, 2005, *Journal of the National Cancer Institute*

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